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Ovarian Reserve Tests for Sub-fertility: When to Intervene

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ABSTRACT

Back ground: During the past two decades , a greater majority of women have been known to plan their pregnancies in the thirties, often because of carrier priorities and as a result, they have to face the consequences of their declining fecundity (reproductive potential). Hence, it was decided to assess the ovarian reserve, which is an estimate of the follicular pool, the production of follicles being the primary function of the ovary. Our work highlights the assessment of the ovarian reserve in sub-fertile women.

Aim: To assess the ovarian reserve in subfertile women by doing hormonal assays and by using ultrasonographic methods.

Materials and Methods: 50 subfertile women of the child-bearing age, without an issue even after 3 years of unprotected sexual acts, were included in this study. The subjects who were under study were divided into two groups. Group 1- sub-fertile women with their ages ranging from 20-25 years and Group 2- sub-fertile women of comparatively older ages, whose ages ranged from 26-33 years. For both the groups, hormones like the Follicular Stimulating Hormone (FSH) and oestradiol (E_2) were measured by ELISA. The Antral Follicular Count (AFC) and the ovarian volume (OV) were measured by transvaginal ultrasound. The correlations between the various parameters were analyzed and the Student's t-test was performed between the two groups by using SPSS.

Results: Statistically significant correlations between age and antral follicular count (AFC), ovarian volume (OV) and FSH were observed. Elevated FSH, and decreased AFC and OV were observed in sub-fertile women of comparatively older ages and their mean values were also statistically different between the two groups.

Conclusion: Women with elevated FSH and E_2 and decreased AFC and OV should be insisted to proceed for Assited Reproductive Technique (ART) as early as possible, irrespective of their ages, as parenthood is undeniably one of the most universally desired goals in adulthood.

Key Words: FSH, Oestradiol ovarian reserve

INTRODUCTION

The production of mature and viable oocytes is the primary function of the female ovary, which should be capable of fertilization, subsequent embryo development and implantation. Women are born with a pre-determined number of ovarian follicles, approximately two million, and these are subsequently reduced by apoptosis and ovulation. So, at birth, the ovary contains a finite number of oocytes which are available for folliculogenesis. This finite number of available oocytes is termed as the ovarian reserve. None of the ovarian reserve tests directly measures the total number of actual oocytes. Rather, it is assumed that the antral follicular count is directly related to the total oocyte pool. The ovarian volume and AFC which can be measured by Trans Vaginal Ultrasonography (TVS), can be useful indicators of the menopausal status and the ovarian function [1]. Day 3 FSH has also been considered as a bio marker of the ovarian reserve, as it provides a glimpse of how well the hypothalamic pituitary gonadal axis is functioning through ovarian feedback to the pituitary [2]. Day 3 oestradiol has also been estimated to assess the ovarian reserve (OR), as oestradiol is a product of the granulosa cells and as it can be considered as a reflection of the follicular activity. The remaining reproductive life time can be assessed by the ovarian reserve test. So, the success of IVF (in vitro fertilization) and ART (Assisted Reproductive Technique) can be predicted by estimating the ovarian reserve. This work highlights the assay of hormones and the ultrasonographic measurement of the ovarian volume and the antral follicular count in sub fertile women of younger ages and comparatively little older ages.

MATERIALS AND METHODS

This study was approved by the institutional ethical committee. Fifty women of the child bearing ages, but without an issue even after 3 years of unprotected sexual acts, were included in this study. An informed consent was obtained from all the participants. The subjects who were under study were divided into two groups. Group 1 (n = 25); sub-fertile women with their ages ranging from 20-25 years. Group 2 (n = 25); sub-fertile women with comparatively older ages which ranged from 26-33 years. The general profile like age, height, weight and body mass index (BMI) were also recorded.

Exclusion Criteria

Thyroid disorders, a history of ovarian surgery, an irregular menstrual cycle and ovarian abnormalities which was assessed by the trans vaginal ultrasonogram method, hormonal conception and male infertility were excluded from this study.

The ovarian volume and the antral follicular count were measured by Transvaginal Ultrasonograph Measurements (TVS).

Trans vaginal ultrasound was performed to measure the number of antral follicles as well as the volume of both the ovaries. It was carried out on the cycle days 3-10. The volume of each ovary was determined by measuring the three perpendicular diameters and by applying the formula for the volume of an ellipsoid. Each ovary was scanned in three dimensions – D1 (longitudinal), D2 (anteroposterior) and D3 (transverse).The volume of each ovary was calculated from the three dimensions by applying the equation for the volume of an ellipsoid (D1*D2*D3*0.523cm^3) [3]. The volumes of both the ovaries were added to calculate the total ovarian volume [4, 5]. All the sonography measurements were done by the same observer by using a 7.5 MHz trans vaginal probe. The examination of the ovary was established by scanning it from the outer to the inner margin. All the follicles which were 2-10 mm in size were measured and counted in each ovary. The sum of both the counts was the antral follicle count.

Hormonal Assay

Both the blood sampling and the ultrasonographic measurements were performed on the same day. Hormones like FSH, LH and E_2 were measured in plasma by ELISA. The specimens were stored at -20^{0}C until they were processed.

RESULTS

A correlation test was done to find the correlation between the variables like, BMI, FSH, E2, AFC, OV and age for both the groups, and the test of significance of the above variables was assessed between the two groups.

From the correlation table, the following results were inferred. Age was inversely related to the antral follicular count (r= -0.557, p = 0.001), which was statistically significant and it was also related to the ovarian volume (r=-0.278, p=0.075), as shown in [Table/Fig-1]. The mean BMI was higher in Group 2 than Group 1. The mean ovarian volume in Group1 was 16.3cm^3 and in Group 2, it was 7.65 cm^3. The mean value of the OV was also statistically significant. Five women in Group 2 had the OV below 3cm^3. The mean follicular number in both the ovaries was 16 in Group 1 and 5.1 in Group2 [Table/Fig-2]. This was also statistically significant. The elevated levels of FSH was more in Group 2 and of these, five women showed an elevation of above 15 IU/l in that group.

	BMI	OV	AFC	FSH	E2
Age	-0.002 0.990	-0.278 0.075.	-0.557 0.001	0.557 0.001	0.034 0.858

[Table/Fig-1]: Correlation of ovarian reserve parameters with age

Screening Parameters	Infertility		Student t-test p-value
	Group 1	Group 2	
Age	22.47±2.40	30.9±2.79	0.000
BMI	23.8±3.3	25.0±3.3	0.337
FSH	4.74±1.4	10.4±8.7	0.015
E2	127.25±48.05	127.8±38.9	0.990
AFC	16.2±4.63	5.1±1.68	0.000
OV	16.3±4.86	7.65±3.63	0.000

[Table/Fig-2]: Test of significane between group 1 and 2
*** Group 1 : Subfertility in younger reproductive age
*** Group 2 : Subfertility in comparatively older age group

DISCUSSION

During the past two decades, a greater majority of women have been known to plan their pregnancy in their thirties, often because of career priorities and as a result, they have to face the consequences of their declining fecundity (reproductive potential). The importance of age in fecundity has been shown by many observations. Although age is an important factor in sub-fertility , it does not exactly predict the reproductive potential. The estimation of serum FSH on day 3 is an indirect method of assessing the ovarian reserve. In one study by Martin et al, no pregnancies were found in the cycles with a day 3 FSH concentration of above 20 IU/ml, while in other studies, age was seen to be a better predictor for the IVF outcome than the basal FSH concentration [6]. Another study by Ahmed Ebbiary et al showed that sub-fertile women with a high FSH concentration had poorer follicular growth in a natural cycle as compared to subfertile women with a normal FSH concentration [7]. Previous studies have revealed that women with normal ovulatory cycles had subtle elevations in the FSH in their early 30s and that these levels tended to increase with age. The day 3 FSH has been believed to represent the basal level or the non-suppressed level of the FSH reserve. This reflects the number and the quality of the oocytes, which at any given age, are available to produce a dominant follicle late in the follicular phase of the menstrual cycle and its value can be elevated due to the occurrence of rapid folliculogenesis [8]. In our study, we noticed an elevated FSH level of above 15 IU/L in sub fertile women of comparatively older age. The authors of this article attributed this decline to a diminished ovarian reserve [9].

Similarly, oestradiol was elevated significantly in the sub-fertile subjects of older ages, which was also an indication of diminished ovarian reserve. The oestradiol concentration, in combination with the basal FSH value and age was found to be a useful predictor of the fertility potential [10]. But some authors found no relationship between the day 3 oestradiol concentration and the pregnancy rates [11].

The number of antral follicles is related to the reproductive age in women with proven fertility and this might also reflect the ovarian reserve [4]. It was found to be less in the sub-fertile population of older ages. The studies by Haadsma et al (2007) showed that the small antral follicles correlated not only with age, but also independently with the results of the various other endocrine ovarian reserve tests like Anti Mullerian Hormone(AMH) [12].

During a woman's life, the ovarian volume changes from 0.7 cm^3 at the age of 10 years to 5.8 cm^3 at the age of 18 years [13]. However, at the age of 40 years, the ovaries tend to decrease in size and they decrease even further after menopause. Syrop et al's (1995) study concluded that the OV might be an important predictor of the OR [5]. But, Tomas et al showed that the ovarian volume was found to be a predictor of the number of growing follicles, but not of the number of recovered oocytes [14]. In our study, the ovarian volume in the sub fertile population of older ages was lesser than that in the subfertile population of younger ages.

Although age is an important factor in sub fertility, it is not very exact in predicting the reproductive potential. Some women will be unable to conceive either early or in their thirties, while others become pregnant in their forties. The ovarian reserve appears to be responsible for these differences [15]. Many tests have been developed to screen the diminished ovarian Reserve.

CONCLUSION

This study strongly emphasize that women with elevated Oestradiol, FSH and low AFC,OV should be insisted to proceed for ART as early as possible, irrespective of their ages. The above mentioned values in women of younger ages also are to be intervened for early counseling to go ahead for ART, as parenthood is undeniably one of the most universally desired goals in adult hood. So, an early intervention and educative counseling will help in reducing the rate of subfertility in our population.

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